

REMARKS

Applicants submitted a Pre-Appeal Brief in this Application on May 30, 2007. On July 11, 2007 the Patent Office issued a Notice of Panel Decision From Pre-Appeal Brief. The Pre-Appeal Panel maintained the rejection of all of the pending claims as presented in the Final Office Action of January 25, 2007 and initially asserted in the Office Action of September 18, 2006. Claims 1-16 presently stand rejected as obvious and unpatentable under 35 U.S.C. § 103(a) over Green et al. (U.S. Patent No. 5,780,601, issued July 14, 1998; hereinafter "Green") in view of Nicholson (U.S. Patent No. 5,681,936, issued October 28, 1997; hereinafter "Nicholson").

Claim 6 has been amended to properly depend from claim 4. It is believed that no new matter has been added and entry of the claim is respectfully requested.

As noted supra, Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as obvious and unpatentable over Green in view of Nicholson.

Claims 1-3 are directed to a process for extracting native or recombinantly-expressed, gram-negative inner membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Claims 4-7 are directed to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Claims 8-12 are directed to a process for extracting lipidated recombinant outer membrane protein P4 (rP4) of *Haemophilus influenzae* from bacterial host cells by differential detergent tangential flow diafiltration.

Claims 13-16 are directed to a process for extracting lipidated recombinant outer membrane protein P6 (rP6) of *Haemophilus influenzae* from bacterial host cells by differential detergent tangential flow diafiltration.

In every one of the claims as pending and as further amended herein, the claimed process of extracting proteins begins with lysis of the bacterial cells containing the proteins **in a fermentation broth**. The Examiner has asserted that, with the exception of tangential flow diafiltration, Green effectively teaches the same method as the present claims (pages 3 and 4 of the Office Action mailed September 18, 2006). Nicholson is then relied upon for the description of tangential flow filtration, which allegedly can be used in Green's process (*citing* Page 4 of the Office Action mailed on January 25, 2007, "the skilled artisan would be motivated to used [sic] tangential flow filtration [TFF] as taught by Nicholson in the method of extracting proteins of Green..."). The Examiner therefore asserts that one "of skill in the art would have been motivated to use TFF in extraction methods...[and that]...[o]ne of skill in the art would have a reasonable expectation of success by combining the prior art references to arrive at the claimed invention." (Office Action of January 25, 2007, page 6)

Applicants respectfully disagree with the Examiner's interpretation of Green and Nicholson because neither of the references, alone or in combination with the other, teach or suggest lysis of bacterial cells **in a fermentation broth**.

The claimed process combines the clarification and extraction processes of particular proteins expressed in bacteria into one unit operation without the need for centrifugation (See Specification e.g., at page 2, lines 5-8). The claimed process accomplishes this task by lysing the bacterial cells **in a fermentation broth**.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). All words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

The U.S. Supreme Court recently clarified the legal standard of obviousness, citing text from an earlier opinion: "[u]nder § 103, scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of

ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." KSR Intern. Co. v. Teleflex Inc., U.S. 2007 (2007 WL 1237837 (U.S.)), at 6, citing *Graham v. John Deere Co. of Kansas City*, 86 S.Ct. 684.

Regarding a motivation to combine prior art references, the Supreme Court stated that an Examiner's analysis must be made explicit. *Id.* at 13. Furthermore, the Supreme Court noted that it can be important to identify a reason to combine elements from different references. *Id.* The Supreme Court warned that "A fact finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *Id.* at 16, citing *Graham*, 393 U.S., at 36. Furthermore, "rejections on obviousness rounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" *Id.*

In the present case, the Examiner has failed to provide an adequate articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. First, the Examiner has failed to provide adequate rationale for combining the two references. Furthermore, assuming, arguendo, that there would be proper motivation to combine the references, the references in fact neither alone or in combination teach or suggest all of the elements of any one of the claims.

Green describes a process of isolating "e" protein from *Haemophilus Influenzae*. The e protein is located in the outer membrane of *Haemophilus Influenzae*. The first step in the process taught by Green uses centrifugation to separate the cells from the cell culture media. Following centrifugation the cells are resuspended in buffer and disrupted to obtain lysed cells. Thus, it is clear from Green that the cells are not lysed in a fermentation broth.

Nicholson describes purification of IL-5 protein, which is secreted into the culture supernatant (*citing* Nicholson, column 11, lines 31 through 33, "Human IL-5 Expressed in Baculovirus-Transfected SF9 Cells is Secreted into the Culture Supernatant and is Entirely Homodimeric."). In Nicholson there is no mention of collecting inner membranes or outer membranes, nor is there any there any description of lysis of the cells, as presently claimed. In addition, even if Nicholson did in fact teach lysing of the cells, or if this lytic step could be provided by Green, Nicholson does not teach or suggest lysis in a fermentation broth. Of course, there is again no motivation to combine Nicholson with Green since Nicholson is directed to isolation of a secreted protein from mammalian cells.

All of the claims are directed to a process for extracting native or recombinantly-expressed, gram-negative proteins from bacteria or bacterial host cells by differential detergent tangential flow diafiltration. The claimed process commences with a step of lysing the bacteria or bacterial host cells in a fermentation broth, followed by diafiltration of the lysed fermentation broth.

With respect to the lysing step, the Examiner asserts that "Green et al. teach that this process is performed in a homogenizer (column 14) since the instant specification teaches that a homogenizer is a microfluidizer []." Page 4 of the Office Action mailed September 18, 2006. No further explanation is provided as to when exactly in Green's process the lysing step occurs, or if it is performed on cells in a fermentation broth, as presently claimed. Additionally, the Examiner fails to point out whether diafiltration occurs on the lysed fermentation broth, as presently claimed.

According to Green, cells are first isolated and removed from the fermentation broth by centrifugation, pelleting and resuspension in a HEPES buffer. Column 14, lines 15-23. It is not until after resuspension that the cells are lysed, at which point they are centrifuged again to remove unbroken cells. Column 14, lines 20-24. Nowhere in Green is there any description of lysing cells in a fermentation broth. Nor does Green describe a subsequent step of diafiltering

lysed cells still present in the fermentation broth. In fact, diafiltration in Green does not occur until after multiple purification steps. Column 14, lines 37-63. Accordingly, Green fails to describe a number of elements of the present claims.

As outlined above, the presently claimed process combines the clarification and extraction processes into one unit operation without the need for centrifugation. Conversely, Green requires multiple units, including columns, resuspensions and centrifugations. The process outlined in Green is onerous, not particularly scaleable, and most importantly, very different from the process of the present claims. The process of the present claims was established to avoid impositions posed by methods such as Green's.

Irrespective of the inclusion of tangential flow filtration, Green and Nicholson do not describe the presently claimed process comprising lysing the bacteria or bacterial host cells in a fermentation broth, followed by diafiltration of the lysed fermentation broth.

Furthermore, Nicholson describes IL-5 purification. Green describes "e" protein isolation (an outer membrane protein). Neither of which describe collection/purification of inner membranes or inner membrane proteins as provided in claims 1-3.

"It is elementary that the claimed invention must be considered as a whole in deciding the question of obviousness." *Litton Indus. Products v. Solid State Systems Corp.* 755 F.2d 158, 225 U.S.P.Q. 34 (Fed.Cir.1985). Particularly, all of the limitations of the claims must be considered, instead of just the select few found in the prior art. There cannot be obviousness where "references fail not only to expressly disclose the claimed invention as a whole, but also to suggest to one of ordinary skill in the art modifications needed to meet all the claim limitations." *Id.* Since the alleged combination of Green and Nicholson describes a process devoid of a number of elements of the present claims, there simply cannot be obviousness under 35 U.S.C. § 103(a).

Withdrawal of the rejection of claims 1-16 is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the application is in condition for allowance. However, the Examiner is invited to contact undersigned if any outstanding issues remain.

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425.



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